

## COMMENTARY

## The consequences of the unregulated cigarette

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This article considers changes in cigarette design in relation to the concept of “dose”, drawing attention to the observation that there is not one smoking related epidemic of lung cancer, but at least two. Squamous carcinoma is declining in parallel with smoking prevalence while adenocarcinoma is increasing in the face of declining smoking prevalence. It is concluded that the adenocarcinoma epidemic is unnecessary and is due substantially to cigarette design changes, including increases in tobacco specific nitrosamines, manipulation of droplet size and ventilated filters. The need for regulation of smoke constituents is emphasised.

The cigarette has been, and is, a virtually unregulated product. Substantial efforts have been made to regulate its marketing with variable degrees of success. However, cigarette design—and the constituents of tobacco and of cigarette smoke—have remained within the control of cigarette manufacturers. There are many well known consequences of this but this paper will focus on some of those issues which have escaped serious attention.

Inculcation of the cigarette as a cause of lung cancer occurred in 1950<sup>1,2</sup> with two outstanding studies yielding convincing evidence. However, this evidence did not persuade any government until backed up by laboratory evidence that painting mouse skin with tobacco tar produced cancers.<sup>3</sup> This persuaded the British Medical Research Council to report that smoking caused lung cancer.<sup>4</sup>

## REGULATION OF MARKETING

In 1962, 12 years after the initial discovery, the Royal College of Physicians<sup>5</sup> recommended abolition of tobacco advertising. However, no country did anything about this until Norway (1975) and Finland (1977) passed laws abolishing such advertising and giving regulators the power of definition of what constituted advertising. Other countries followed suit with partial and progressively increasing bans but major populations in the European Union and the United States are precluded from much of this action by constitutional or legal factors. In 2006 advertising is severely restricted or absent in a significant number of countries, but this is still circumvented by the persistence of global tobacco advertising in such forms as Formula One television.

## REGULATION OF THE CIGARETTE AND ITS SMOKE CONSTITUENTS

The European Union restricts tar and nicotine levels and requires disclosure of additives and their toxicology, but does not attempt to restrict the galaxy of toxicants in the cigarette or its smoke. Attempts to achieve regulatory capture of the cigarette as a nicotine delivery device in the United States have, so far, failed.<sup>6</sup> No other country has before it legislation to control specific smoke-born toxicants or any other aspects of cigarette design, and it is a fair generalisation that the tobacco control community has made only minor efforts to achieve this and is divided over its merits. This situation represents a failure which has had serious consequences that are poorly appreciated. The modern cigarette has a number of design features that contribute to avoidable deleterious effects.

## GENERATIONAL AND GENDER ISSUES

It is necessary to understand that men started smoking en masse several decades before women.<sup>4</sup> As a result they smoked a different generation of cigarettes with different chemical composition. This is important when considering whether responses by the sexes to tobacco differ because of constitutional and genetic factors or are more substantially related to smoke chemistry.

## REFLECTIONS ON THE CONCEPT OF “DOSE” AND THE CHANGING CIGARETTE

Over time the cigarette (plus the packet and the pack-year) has been used as the basic unit of dose and has proven a satisfactory unit for the epidemiological studies arising out of the cigarettes smoked in the first half of the 20th century, correlating well with mortality and incidence of smoking associated disease arising from their use. This is especially true of lung cancer for which other risk factors are minor. However, changes starting in the 1950s have altered the situation. While the detailed “recipes” for individual brands are carefully guarded secrets, some major developments have rendered the modern cigarette less suitable as an estimate of dose. Quite apart from the fact that a modern cigarette is more likely to weigh 0.7 g instead of the 1–1.2 g of the cigarette of the ‘50s, numerous alterations to cigarette design and composition

**Abbreviations:** FTC, Federal Trade Commission; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; PAHs, poly aromatic hydrocarbons; TSNA, tobacco specific nitrosamines

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have caused the content of mainstream and sidestream smoke to be greatly different.

Starting with early model filters in the '50s, manufacturers<sup>7</sup> introduced reconstituted leaf, expanded leaf (various techniques), approximately 600 additives, different blends, different systems for curing the tobacco (including use of propane gas as a drying agent), variously porous and impregnated papers, ventilated filters and many other design changes. Many of these were aimed at reducing the yields of tar and nicotine as measured by the Federal Trade Commission (FTC) system, but nevertheless providing sufficient doses of nicotine to the smoker.<sup>8</sup>

Indices of "national" dose such as smoking prevalence, measured by questionnaire based on random sampling; and per capita consumption, a measure concocted from a variety of sources including manufacturers reports and taxation figures, give a general picture of national "dose" but are flawed to a variable degree depending on the sophistication of the country and the contribution of such elements as smuggling. Measures of sales weighted "tar" are generally misleading,<sup>8</sup> except that they reflect quite well the trends in levels of poly aromatic hydrocarbons (PAHs) since this group of carcinogens correlates relatively well<sup>9</sup> with "tar". None of the published measures offer even a remote indication of the dose of carcinogenic tobacco specific nitrosamines (TSNAs) which varies greatly within and between brands.<sup>10 11</sup> Furthermore, none of the measures can give a reasonable indication of a ranking on the scale of carcinogenicity<sup>12</sup> of individual brands or national "dose". So quantitative measures of dose do not reflect qualitative changes, nor do they reflect the major differences in individual smoking topography patterns seen in the real world.<sup>13</sup>

Of course, one of the most accurate historical measures of the "dose", reflecting what has actually been taken, is the outcome of the dose over time. Perhaps the best indices of long term national dose are lung cancer incidence and mortality. It is within this parameter that histological changes that reflect the qualitative changes in cigarettes can be seen.

## MODERN CIGARETTE DESIGN AND ITS CONSEQUENCES

The modern, low tar cigarette has a number of characteristics that militate against public health. Essentially these are designed to make the delivery of nicotine to the brain more efficient while, at the same time, achieving low measured amounts of tar and nicotine under the (FTC) system. They include elasticity (facilitation of compensatory smoking), ease of smoking, enhancement of nicotine absorption, and changes in smoke chemistry.

### Ventilated filters

The role of filter ventilation has been important in providing low machine measured yields of tar and nicotine but also in facilitating increased depth of inhalation, which together with increased puff frequency (and sometimes cigarette numbers), is defined as compensatory smoking.<sup>14</sup> Without filter ventilation deep inhalation is harder. Deep inhalation is also assisted by production of optimal droplet size particles<sup>15</sup> thus exposing the periphery of the lung to greater volumes of smoke and delivering both nicotine and the carcinogenic mix with maximum efficiency. Ventilation of filters can also lead to changes in smoke chemistry.<sup>16</sup>

### Ease of smoking

The early low additive cigarette was not easy to smoke or to learn to smoke. Qualities such as "after taste, bitterness, mouth sensation and throat scratch" are now approached by the use of techniques such as two-stage blending of tobacco,

puffing the tobacco, paper specifications, and use of humectants, flavourants and filtration. The result is a "smoother" cigarette that also tastes "lighter".<sup>14 17</sup> It is a reasonable presumption that the modern cigarette is both easier to smoke and easier to learn to smoke.

### Nicotine absorption

Nicotine is addictive and can be made more efficiently so by use of chemical techniques that increase the unprotonated or "free" nicotine component of the smoke. Use of ammonia technology increases pH and, as a consequence, free nicotine levels which have the effect of increasing speed of absorption and a better "kick".<sup>18</sup> It seems likely that modern cigarettes are more efficiently addictive than those of the first half of the 20th century.

### Changes in smoke chemistry

The chemistry of cigarette smoke has changed dramatically since the original major studies linking smoking to lung cancer, which reflected the effects of cigarettes manufactured in the first half of the century. This has been extensively documented by Hoffmann<sup>7</sup> who describes increases in nitrogen oxides, benzene, and TSNAs but decreases in benzpyrene, acetaldehyde, catechol and phenol over the second half of the 20th century. These changes, however, are not consistent among brands which may differ greatly in detailed composition, with fivefold differences in individual compounds being quite common.<sup>12</sup>

The role of TSNAs, particularly 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), is germane to the issues discussed here. NNK is a systemic carcinogen in animals, inducing adenocarcinoma of the lung in rats, hamsters, and mice, independent of the route of administration. DNA adducts of NNK have been detected in smokers and lung cancer patients.<sup>19</sup> While information is variable for other countries, NNK levels have increased in US cigarettes over recent decades. By contrast, levels of benz(a)pyrene have decreased.<sup>20</sup>

### The adenocarcinoma epidemic

The relationship between cigarette smoking and lung cancer has been clearly established over time.<sup>4 21</sup> The pattern of lung cancer incidence and mortality closely reflects the smoking of previous decades. Men started smoking before women. Early in the epidemic the predominant histological type was squamous cell but later in the epidemic adenocarcinoma became more common than squamous. Small cell carcinoma has tended to track with squamous cell carcinoma. Adenocarcinoma was always predominant among women.

Several factors complicate this analysis. The accuracy of histological diagnosis has been questioned and may have changed over time. The published data relates to different time periods so may reflect different changes in cigarette design. While there is an abundance of data relating to the histology of lung cancer in the United States, fewer studies cover other countries. In the United States there is good prevalence data over time but this is also not universal globally, particularly for the '50s, '60s and '70s. Also lung cancer in Asian women is often not associated with smoking and adenocarcinoma is the predominant type seen.

### Accuracy of histological diagnosis

Careful review articles have addressed this specific issue and concluded that the swing to adenocarcinoma is unlikely to be an artefact of diagnosis.<sup>22-24</sup>

### The effect of time periods

Studies considered here have accumulated figures from a time period and show the swing to adenocarcinoma over that period. The change was noted in the United States in the '70s

and has been consistently observed since.<sup>15 24–33</sup> Although other countries have experienced the same trends<sup>34–39</sup> there is less supporting information about changes in prevalence and smoke composition to match this.

Further, while there has been a decline in the incidence of squamous carcinoma in US males, there is evidence of an absolute increase in incidence of adenocarcinoma into the 1990s,<sup>24 27 28 39 40</sup> which may have now peaked in men.<sup>41</sup> The important fact to note is that the decline in squamous carcinoma is as expected and consistent with the decline in smoking prevalence (and in tar yields) that took place among US men in the 1960s. However, the increase in incidence of adenocarcinoma (in both sexes) has taken place in the face of falling smoking prevalence and tar yields, which is the opposite of what would be expected, and can only be explained by changes in the composition of cigarette smoke.

## DISCUSSION

It seems, from the above, that there is not one epidemic of lung cancer but (at least) two. One (squamous) has declined but the other (adenocarcinoma) has increased, very often in the face of declining levels of smoking prevalence, tar content and per capita consumption, for which the evidence is strongest in US males. This strongly suggests a different causal basis, and it is extremely likely that this lies within the qualitative differences between modern cigarettes and their predecessors. The adenocarcinoma epidemic can reasonably be described as unnecessary.

The question of whether gender has an effect on susceptibility to tobacco induced cancer has been raised with uncertain outcome. Several studies suggested this to be the case.<sup>42–44</sup> However three very large cohort studies<sup>45–47</sup> do not support this contention. The same argument has been adduced to explain the predominance of adenocarcinoma among women.<sup>48</sup> However, not only have women smoked cigarettes of a different generation to men, they have smoked different brands,<sup>49 50</sup> so exposure to the spectrum of tobacco carcinogens has been different.

Without disregarding the genuine possibility of gender differences, changes in cigarette design also offer a plausible explanation. Of the three major factors at work, deeper inhalation due to compensatory smoking, better absorption and exposure of peripheral lung due to efficiently tailored droplet size are clearly important. Changes in the carcinogenic mix of cigarette smoke, particularly increases in nitrosamine content, are likely to play a major part.

Trends in nitrosamine content are not available; however, it is known that American style blends have had increased levels in recent decades and that the US tobacco industry has recently addressed the problem and is aiming to reduce this component of smoke, at least in the United States.<sup>51</sup> The work of Fischer<sup>11</sup> and others<sup>10</sup> has shown notable differences in nitrosamine yields between countries and brands, and within brands, but generalisations as to long term trends are difficult to make, with the exception of the United States.

Although speculative, it seems likely that regular smoking of a brand containing 733 ng per cigarette of NNK is more likely to result in adenocarcinoma of the lung than equivalent usage of one containing 433 ng per cigarette. Such brands existed on the US market in the 1990s<sup>12</sup> while in other countries levels below 100 ng per cigarette are seen.

The most plausible explanation for the adenocarcinoma epidemic is change in cigarette design, which is under the control of the manufacturers, not government regulators. It is inconceivable that any regulator would have permitted increases in any class of carcinogen and entirely likely that a programme of controlled reduction would have been established (as with automobile exhausts), had regulators had power and information. Unless cigarette design is

controlled we face a replay of the mistakes made over the low tar programme; where the public health establishment encouraged reduction in tar but left the manipulation of the change to an uncontrolled manufacturing industry<sup>52</sup> with the consequences discussed here.

The historical mistake has been to regard the international tobacco industry as a normal commercial enterprise when it is, and should be treated as, a drug manufacturer.<sup>53</sup> Once this change in mindset is achieved we can expect the cigarette to be treated as a drug delivery device and to be regulated in the same, or a similar, framework as pharmaceutical drugs. This would necessarily bring focus onto the way in which nicotine is manipulated and delivered, as well as onto the chemical minestrone of toxicants that accompanies it into smoker's lungs.

This change in focus would appear inevitable and, since it involves the controversial concept of harm reduction, will require rigorous monitoring of advertising claims made for newer cigarettes. Clearly standards (upper limits) should be set for key compounds in smoke. This would have the relatively immediate effect of reducing exposure, but only long term monitoring will demonstrate whether these reductions translate into disease reduction. Hence, any advertising claims would require controls like those imposed on pharmaceuticals.

Under no circumstances should we be deluded into thinking that regulation is a pathway to a safe cigarette. While the above suggestions ought to reduce carcinogenicity, current knowledge is not encouraging in relation to heart disease and other tobacco induced causes of illness and death. So the basics of current policy—prevention of initiation and increased cessation activity—will remain so.

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